These organizations relied on data from animal and human studies demonstrating nicotine's ability to produce addiction. Definitive studies had not been conducted before 1980. During the 1980's and 1990's, however, there was an explosion of new studies on nicotine designed to determine whether nicotine is addictive. Thus, new studies, not available when the ASH petitions were decided, now conclusively demonstrate that nicotine has the characteristics of an addictive drug.[1164] The new data support the following findings, among others:

- Nicotine is self-administered by animals, demonstrating that it is a "positive reinforcer" (i.e., it causes repeated, compulsive use of the drug), one of the hallmark characteristics of addictive drugs;[1165]

[1164] *See* section II.A.3., above, for a complete description of these studies and their significance in assessing nicotine's addictiveness.

[1165] Goldberg SR, Spealman RD, Goldberg DM, Persistent behavior at high rates maintained by intravenous self-administration of nicotine, *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

Goldberg SR, Spealman RD, Maintenance and suppression of behavior by intravenous nicotine injections in squirrel monkeys, *Federation Proceedings* 1982;41(2):216-220. *See* AR (Vol. 39 Ref. 52).

Spealman RD, Goldberg SR, Maintenance of scheduled-controlled behavior by intravenous injections of nicotine in squirrel monkeys, *Journal of Pharmacology and Experimental Therapeutics* 1982;223(2):402-408. *See* AR (Vol. 42 Ref. 146).

Risner ME, Goldberg SR, A comparison of nicotine and cocaine self-administration in the dog: fixed-ratio and progressive-ratio schedules of intravenous drug infusion, *Journal of Pharmacology and Experimental Therapeutics* 1983;224(2):319-326. *See* AR (Vol. 42 Ref. 119).

Cox BM, Goldstein A, Nelson WT, Nicotine self-administration in rats, *British Journal of Pharmacology* 1984;83:49-55. *See* AR (Vol. 8 Ref. 93-1).

Slifer BL, Balster RL, Intravenous self-administration of nicotine: with and without schedule-induction, *Pharmacology, Biochemistry and Behavior* 1985;22:61-69. *See* AR (Vol. 8 Ref. 93-3).

Corrigall WA, Coen KM, Nicotine maintains robust self-administration in rats on a limited-access schedule, *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 347 Ref. 5495).

- Consistent with the animal self-administration data, nicotine serves as a positive reinforcer in humans;[1166]
- Nicotine is psychoactive, serving as a discriminative stimulus in animals[1167] and producing subjective effects in humans;[1168]

[1166] Henningfield JE, Miyasoto K, Jasinski DR, Cigarette smokers self-administer intravenous nicotine, *Pharmacology, Biochemistry and Behavior* 1983;19:887-890. *See* AR (Vol. 39 Ref. 71).

Surgeon General's Report, 1988, at 192. *See* AR (Vol. 129 Ref. 1592).

[1167] Stolerman IP, Discriminative stimulus effects of nicotine in rats trained under different schedules of reinforcement, *Psychopharmacology* 1989;97:131-138. *See* AR (Vol. 8 Ref. 90-6).

Craft RM, Howard JL, Cue properties of oral and transdermal nicotine in the rat, *Psychopharmacology* 1988;96:281-284. *See* AR (Vol. 74 Ref. 115).

Stolerman IP, Garcha HS, Pratt JA, *et al.*, Role of training dose in discrimination of nicotine and related compounds by rats, *Psychopharmocology* 1984;84:413-419. *See* AR (Vol. 8 Ref. 90-5).

Garcha HS, Goldberg SR, Reavill C, *et al.*, Behavioural effects of the optical isomers of nicotine and nornicotine, and cotinine, in rats, *British Journal of Pharmacology* 1986;88:298. *See* AR (Vol. 38 Ref. 44).

Takada K, Swedberg MDB, Goldberg SR, *et al.*, Discriminative stimulus effects of intravenous l-nicotine and nicotine analogs or metabolites in squirrel monkeys, *Psychopharmacology* 1989;99:208-212. *See* AR (Vol. 43 Ref. 153).

[1168] Henningfield JE, Miyasato K, Jasinski DR, Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine, *Journal of Pharmacology and Experimental Therapeutics* 1985;234:1-12. *See* AR (Vol. 39 Ref. 69).

Pomerleau CS, Pomerleau OF, Euphoriant effects of nicotine in smokers, *Psychopharmacology* 1992;108:460-465. *See* AR (Vol. 87 Ref. 426).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state, *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmacology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

- Nicotine reliably produces a withdrawal syndrome;[1169]
- Nicotine, like other addictive drugs (e.g., cocaine, amphetamine, and morphine), produces its addictive effects by actions increasing dopamine concentrations within the mesolimbic system of the brain.[1170]

In addition to the core studies demonstrating nicotine's addictiveness, other widely publicized information relevant to the finding that nicotine in cigarettes and smokeless tobacco has significant pharmacological effects has become available since 1980. This new information includes, for example:

- Studies showing that nicotine produces EEG effects on the brain that are reproducible and are known to be associated with changes in mood and alertness;[1171]

[1169] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

West RJ, Jarvis MJ, Russell MAH, *et al.*, Effect of nicotine replacement on the cigarette withdrawal syndrome, *British Journal of Addiction* 1984;79(2):215-219. *See* AR (Vol. 8 Ref. 102-1).

Hughes JR, Hatsukami D, Signs and symptoms of tobacco withdrawal, *Archives of General Psychiatry* 1986;43:289-294. *See* AR (Vol. 8 Ref. 102-2).

Hughes JR, Higgins ST, Hatsukami D, Effects of abstinence from tobacco: a critical review, *Research Advances in Alcohol and Drug Problems* 1990;10:317-398, at 381-382. *See* AR (Vol. 535 Ref. 96, III.G).

[1170] Clarke PBS, Mesolimbic dopamine activation—the key to nicotine reinforcement? *CIBA Foundation Symposium* 1990;152:153-168. *See* AR (Vol. 3 Ref. 19-2).

Di Chiara G, Imperato A, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, *Proceedings of the National Academy of Sciences of the United States of America* 1988;85:5274-5278. *See* AR (Vol. 75 Ref. 128).

Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

[1171] Norton R, Brown K, Howard R, Smoking, nicotine dose and the lateralisation of electrocortical activity, *Psychopharmacology* 1992;108:473-479. *See* AR (Vol. 3 Ref. 22).

Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

- Data that have led expert bodies to conclude that marketed cigarettes and smokeless tobacco deliver pharmacologically active (addicting) doses of nicotine;[1172]
- Studies showing that nicotine exposure causes an increase in the number of nicotinic receptors in the central nervous system, a phenomenon associated with development of tolerance to the effects of nicotine;[1173] and
- Studies done in the 1980's and 1990's showing that nicotine replacement therapies are effective in assisting smoking cessation, which provide additional evidence that nicotine is the ingredient in cigarettes that causes addiction.[1174]

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

Golding JF, Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving, *Pharmacology, Biochemistry and Behavior* 1988;29:23-32. *See* AR (Vol. 3 Ref. 23-3).

[1172] Department of Health and Human Services, Public Health Service, *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General, 1986,* NIH Publication No. 86-2874 (Bethesda MD: DHHS, PHS, 1986). *See* AR (Vol. 128 Ref. 1591).

Surgeon General's Report, 1988, at 13-17. *See* AR (Vol. 129 Ref. 1592).

Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products," Aug. 2, 1994, at 336-342. *See* AR (Vol. 255 Ref. 3445).

[1173] Marks MJ, Burch JB, Collins AC, Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Department of Health and Human Services, Centers for Disease Control and Prevention, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Atlanta: USDHHS, 1994), at 32-33. *See* AR (Vol. 133 Ref. 1596).

Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (-)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[1174] *See*, e.g., Fiore MC, Smith SS, Jorenby DE, *et al.*, The effectiveness of the nicotine patch for smoking cessation: a meta analysis, *Journal of the American Medical Association* 1994;271:1940-1947. *See* AR (Vol. 6 Ref. 64-1).

On the basis of the voluminous new data on nicotine that have become available since 1980 and the virtually universal consensus that has emerged from these data that nicotine is highly addictive and produces other significant pharmacological effects, FDA has concluded that nicotine's addictive and other pharmacological effects and uses are so widely recognized that they must be considered foreseeable to a reasonable tobacco manufacturer. The conclusion that nicotine's effects are so widely known and foreseeable would have been impossible when FDA last considered whether to regulate cigarettes because neither the definitive data nor the scientific consensus existed.

b. Since 1980, Evidence Has Become Available That Consumers Use Tobacco Predominantly for Its Pharmacological Effects

As described in section II.B., above, evidence that consumers use a product predominantly or nearly exclusively for its pharmacological effects permits the Agency to conclude that the product is intended to affect the structure or function of the body. The Agency recognizes that for many years there was general awareness of the difficulty smokers experienced in trying to stop smoking. Since 1980, however, scientific evidence has shown that the vast majority of smokers and users of smokeless tobacco use cigarettes and smokeless tobacco to satisfy addiction or for other pharmacological effects. The evidence that has emerged since the last time that FDA considered whether to regulate cigarettes includes, for example:

- Evidence that 77% to 92% of smokers and as many as 75% of young regular smokeless tobacco users are addicted;[1175]

See appendix 1 to Jurisdictional Analysis, at 62-83. *See* AR (Vol. 1 Appendix 1).

[1175] Hughes JR, Gust SW, Pechacek TF, Prevalence of tobacco dependence and withdrawal, *American Journal of Psychiatry* 1987;144(2):205-208. *See* AR (Vol. 66 Ref. 4).

- Evidence that a higher percentage of people who use cigarettes become addicted than people who use other addictive drugs, including cocaine and heroin;[1176]
- Evidence that, of young people aged 10 to 22 years, 72.8% of daily smokers and 53.8% of daily users of smokeless tobacco use tobacco to "relax" themselves;[1177] and
- Data demonstrating that many smokers believe that smoking helps them control their weight and that continued smoking is related to concerns about weight gain.[1178]

This new evidence, together with some existing evidence that smokers use cigarettes to control their moods, is sufficient to demonstrate that cigarette smokers and smokeless tobacco users consume tobacco predominantly to satisfy addiction, alter moods, and control weight. FDA would have been unable to reach this conclusion in 1980. At that time there was no evidence on the proportion of smokers and smokeless tobacco users who were addicted to tobacco (indeed, there was no agreement that nicotine was

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Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. *See* AR (Vol. 13 Ref. 150).

Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction*, 1993;88:689-696. *See* AR (Vol. 13 Ref. 149).

Hale KL, Hughes JR, Oliveto AH, *et al.*, Nicotine dependence in a population-based sample, in *Problems of Drug Dependence, 1992*, NIDA Research Monograph 132 (Washington DC: Government Printing Office, 1993). *See* AR (Vol. 39 Ref. 60).

Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

[1176] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[1177] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescent and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750, at 747. *See* AR (Vol. 43 Ref. 162).

[1178] Surgeon General's Report, 1988, at 438-441. *See* AR (Vol. 129 Ref. 1592).

addictive), and evidence on the use of tobacco for other pharmacological effects was insufficient to conclude that cigarettes and smokeless tobacco are consumed predominantly for their pharmacological effects.

c. Since 1980, Evidence Has Become Available Demonstrating That Tobacco Manufacturers Actually Intend Their Products To Affect the Structure and Function of the Body

As described in section II.C., above, FDA may also find that cigarettes and smokeless tobacco are "intended to affect the structure or any function of the body" on the basis of objective evidence that the manufacturers of these products actually intend them to affect the structure or function of the body. Such objective evidence includes company-funded research and internal statements showing that the manufacturers know or have knowledge of facts that would give them notice that consumers are using cigarettes and smokeless tobacco to obtain nicotine's pharmacological effects. Relevant objective evidence of intent also includes evidence that manufacturers have taken actions to ensure that consumers obtain pharmacologically active doses of nicotine from marketed tobacco products.

As discussed in section II., above, FDA, congressional, and other investigations into tobacco products over the last two years have uncovered a wealth of documents from a wide range of tobacco companies, the vast majority of which had not been made public by the tobacco industry. Although in some cases these documents date back to the early 1960's, they have not been available to the public or to FDA until recently. As described in greater detail in section II., above, the newly discovered documents reveal the following facts, among others, none of which were known when FDA last considered its jurisdiction over cigarettes:

- Statements from tobacco company researchers and executives show that the tobacco industry knows that nicotine is a drug, that consumers use tobacco primarily for the pharmacological effects of nicotine, and that nicotine is addictive;
- The tobacco industry has conducted extensive and sophisticated research to understand precisely how nicotine affects the structure and function of the body;
- The tobacco industry has conducted product development research on how to manipulate nicotine delivery from cigarettes to ensure that cigarettes deliver pharmacologically active doses of nicotine;
- The tobacco industry has manipulated the delivery of nicotine from marketed cigarettes to maintain and enhance the delivery of nicotine from low-yield cigarettes through the use of higher nicotine tobaccos, chemicals added to tobacco, and selective filtration and ventilation;
- The smokeless tobacco industry has manipulated the delivery of nicotine from smokeless tobacco to create product lines with graduating nicotine deliveries, and at least one company has used a "graduation strategy" designed to encourage new users to begin with the lowest nicotine products and then graduate to the higher nicotine products.

These facts, among others, demonstrate that the tobacco industry knows that consumers use their products to obtain nicotine's pharmacological effects and that they have taken specific actions to facilitate that use. FDA has concluded on the basis of this new evidence that tobacco manufacturers actually intend cigarettes and smokeless tobacco to affect the structure or function of the body.

Almost none of the evidence of tobacco industry knowledge and actions was available to the Agency when it last declined to exercise jurisdiction over cigarettes without claims. One comment argues that FDA's earlier decision not to regulate tobacco products without claims is directly attributable to the tobacco industry's withholding of material documents. Indeed, Joseph Califano, who was Secretary of the Department of Health, Education, and Welfare at the time that FDA last declined to regulate cigarettes, has testified under oath before Congress that he would have "moved to regulate" had he known what FDA now knows about the internal tobacco company documents.[1179] He further testified that he had consulted with both President Jimmy Carter and then Surgeon General Julius Richmond and both agreed that, had this evidence been available, they too would have moved to regulate.[1180] FDA agrees with several comments that argue that not allowing FDA to change its position on the basis of this new evidence would reward the tobacco industry for its long-successful efforts to conceal its knowledge and actions related to nicotine.

FDA's decision to change its previous position that cigarettes and smokeless tobacco are not intended to affect the structure or function of the body is thus based on an overwhelming body of new evidence that has become available since FDA last considered this issue. The new evidence persuades the Agency to conclude that its previous position is no longer consistent with the relevant facts and should be changed. FDA's lengthy description of the new evidence in the Jurisdictional Analysis and in this document

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[1179] *Regulation of Tobacco Products (Part 2): Hearings Before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives*, 103d Cong., 2d Sess. 166 (May 17, 1994). *See* AR (Vol. 708 Ref. 2).

[1180] *Id.*

provides a reasoned explanation for its change in position. The Agency's new position is therefore entitled to deference. *American Trucking,* 387 U.S. at 416.

C. NEW EVIDENCE THAT NICOTINE ADDICTION IS A PEDIATRIC DISEASE PERMITS EFFECTIVE REGULATORY INTERVENTION

In addition to the new evidence establishing that cigarettes and smokeless tobacco are "intended to affect the structure or any function of the body," new information developed since 1980 on young people's use of tobacco products shows that FDA's regulatory resources can be used effectively to reduce tobacco-related disease and death. Recent data establish that most of the people who suffer the adverse health consequences of using cigarettes and smokeless tobacco begin tobacco use in childhood and adolescence. Moreover, new data suggest that anyone who does not begin tobacco use in childhood or adolescence is unlikely ever to begin. This information provides a unique public health opportunity to substantially reduce the more than 400,000 deaths from tobacco use each year in the United States. If children and adolescents can be successfully prevented from initiating tobacco use and becoming addicted to cigarettes and smokeless tobacco, they are unlikely to begin tobacco use later in life, thereby preventing the onset of tobacco-related disease and premature death.

Major recent reports have emphasized the effectiveness of legislative and regulatory interventions that focus on restricting children's access to tobacco products and on reducing the appeal of tobacco products to youth.[1181] Before the importance of youth-centered interventions was identified, the regulatory approaches available under the Act to

[1181] Department of Health and Human Services, Office on Smoking and Health, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington, DC: Government Printing Office, 1994) (hereinafter cited as Surgeon General's Report, 1994). *See* AR (Vol. 133 Ref. 1596).